J. Vet. Med. B 51, 374–379 (2004)
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ISSN 0931–1793

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Evidence of an Association Between Use of Anti-microbial Agents in Food Animals and Anti-microbial Resistance Among Bacteria Isolated from Humans and the Human Health Consequences of Such Resistance

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Summary

Several lines of evidence indicate that the use of anti-microbial agents in food animals is associated with anti-microbial resistance among bacteria isolated from humans. The use of anti-microbial agents in food animals is most clearly associated with anti-microbial resistance among *Salmonella* and *Campylobacter* isolated from humans, but also appears likely among enterococci, *Escherichia coli* and other bacteria. Evidence is also accumulating that the anti-microbial resistance among bacteria isolated from humans could be the result of using anti-microbial agents in food animals and is leading to human health consequences. These human health consequences include: (i) infections that would not have otherwise occurred and (ii) increased frequency of treatment failures and increased severity of infection. Increased severity of infection includes longer duration of illness, increased frequency of bloodstream infections, increased hospitalization and increased mortality. Continued work and research efforts will provide more evidence to explain the connection between the use of anti-microbial agents in food animals and anti-microbial-resistant infections in humans. One particular focus, which would solidify this connection, is to understand the factors that dictate spread of resistance determinants, especially resistant genes. With continued efforts on the part of the medical, veterinary and public health community, such research may contribute to more precise guidelines on the use of anti-microbials in food animals.

Introduction

As in human medicine, the use of anti-microbial agents in food animals creates a selective pressure for the emergence and dissemination of anti-microbial-resistant bacteria. Anti-microbial resistance resulting from the use of anti-microbial agents in food animals may occur among animal pathogens, commensal bacteria that are present in food-producing animals and human pathogens that have food animal reservoirs. These resistant bacteria may be transferred from food animals to humans by various means – through the food supply and following contact with animals and their manures. The transfer of resistant bacteria from food animals to humans is most evident in, but not limited to, human pathogens which have food animal sources, such as *Salmonella* which has important reservoirs in cattle, chickens, pigs and turkeys, and *Campylobacter jejuni* which has reservoirs in chickens and turkeys.

This article reviews evidence of an association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans. It addresses evidence that such anti-microbial resistance results in human health consequences. It also summarizes the conclusions of previous World Health Organization (WHO), Food and Agriculture Organization (FAO) and the Office International des Épizooties (OIE) reports concerning the human health consequences of use of anti-microbial agents in food animals.

Review of Association Between Use of Anti-microbial Agents in Food Animals and Anti-microbial Resistance Among Bacteria Isolated from Humans

An association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans is most evident among *Salmonella* and *Campylobacter*, but is also present among enterococci, *Escherichia coli* and other bacteria. The awareness of an association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans is longstanding. In the UK, for example, such a conclusion was reached by the 'Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine', chaired by Prof. Swann (Swann et al., 1968).

Several lines of evidence demonstrate an association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans including: (i) outbreak investigations; (ii) epidemiological investigations of sporadic infections; (iii) field studies; (iv) case reports; (v) ecological and temporal associations; and (vi) molecular subtyping comparing isolates from human and non-human sources. Numerous studies provide support for one or more of the lines of evidence demonstrating an association between use of anti-microbial agents in food animals and anti-microbial resistance in humans. This evidence has been recently summarized (Angulo et al., 2000; Swartz, 2002).

Outbreak investigations

Although outbreaks represent a fraction of the cases of infections caused by food-borne pathogens such as *Salmonella*, much insight into the epidemiology of food-borne diseases has been provided through the investigations. Several outbreak investigations of anti-microbial-resistant *Salmonella* infections in humans have combined epidemiological fieldwork and

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laboratory subtyping techniques to trace anti-microbial-resistant *Salmonella* through the food distribution system to farms. Use of anti-microbial agents on the farms was found to be associated with the anti-microbial resistance in the *Salmonella* isolated from humans. Among the most notable outbreak investigations have been the tracing of human tetracycline-resistant *Salmonella* infections to the 'top-dressing' of cattle feed with tetracycline (Holmberg et al., 1987) and the tracing of human chloramphenicol-resistant *Salmonella* infections to the illegal use of chloramphenicol on dairy farms (Spika et al., 1987). A review of outbreaks of *Salmonella* infections indicated that outbreaks caused by anti-microbial-resistant *Salmonella* were more likely to have a food animal source than outbreaks caused by anti-microbial-susceptible *Salmonella* (Holmberg et al., 1987). More recently, an outbreak of human nalidixic acid-resistant *Salmonella* Typhimurium DT104 infections in the UK was traced to a dairy farm where fluoroquinolones were used in the cattle the month prior to the outbreak (Walker et al., 2000).

Epidemiological investigations

A case–control study in the USA of persons infected with fluoroquinolone-resistant *Campylobacter* found that they were more likely to have eaten chicken or turkey outside the home than well controls. As chicken and turkey is not imported into the USA, this finding provides evidence that poultry is an important source of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in the USA (Kassenborg et al., 2004).

Several recent epidemiological investigations of sporadic cases of human *Salmonella* infections have demonstrated that persons with anti-microbial-resistant infections are more likely to have visited or lived on a farm before the onset of illness than persons infected with anti-microbial-susceptible infections. These findings have been demonstrated in a case–control study of anti-microbial-resistant *S.* Typhimurium DT104 infections (Glynn et al., 2004) and multidrug-resistant *Salmonella* Newport infections (Gupta et al., 2003).

Field studies

Levy et al. (1976)) conducted prospective field experiments to demonstrate how anti-microbial use in food animals selects for the emergence and dissemination of anti-microbial-resistant determinants. They found that the tetracycline resistance among *E. coli* in fecal samples from chickens increased within 1 week of introduction of animal feed containing tetracycline. Importantly, as long as the chicken feed contained tetracycline, the proportion of tetracycline-resistant intestinal coliforms was also greater among members of the immediate farm family and remained higher than intestinal coliforms from neighbourhood control families.

As streptothricin anti-microbial agents had not been used either in human or in veterinary medicine, the introduction of nourseothricin, a novel streptothricin anti-microbial agent, into swine production as a growth promoter in the former East Germany provided a unique opportunity to see the outcome of using anti-microbial growth promoters. Investigators were able to see how use of nourseothricin selected for the emergence of anti-microbial resistance in bacteria of pigs, disseminated resistant bacteria to humans and transferred resistant determinants to other human bacteria, including pathogens. Shortly after nourseothricin started to be used as a growth promoter in pigs, coliform organisms containing plasmids conferring nourseothricin resistance were frequently found in faecal isolates of pigs and employees of the pig farms. Within 2 years, similar coliform organisms with plasmids carrying nourseothricin-resistant determinants were found among family members of the employees of the pig farms and in outpatients in adjacent communities (Hummel et al., 1986). Nourseothricin resistance was subsequently detected in human *Salmonella* and *Shigella* isolates (Witte et al., 2000). As *Shigella* was not found in the intestinal tract of swine, these events provide important evidence of emergence of nourseothricin resistance in the intestinal tract in treated pigs, transfer of nourseothricin-resistant bacteria to humans and horizontal transfer of nourseothricin-resistant determinants within the intestinal tract of humans.

Case reports

There are several individual case reports of farmers, members of their families or other persons who have become directly exposed to anti-microbial-resistant bacteria from food animals. For example, the first reported case of domestically acquired ceftriaxone-resistant *Salmonella* in the USA involved the child of a veterinarian. Before the child's illness, the father was treating several herds for *Salmonella*. Ceftriaxone-resistant and ceftriaxone-susceptible *Salmonella* were isolated from ill cattle treated by the veterinarian. These isolates and the child's ceftriaxone-resistant isolate were very similar by pulsed-field gel electrophoresis (PFGE). It appears likely that the *Salmonella* strain developed ceftriaxone resistance in the cattle and then was transmitted to the child (Fey et al., 2000).

Ecological and temporal associations

In countries, like Denmark, with surveillance data on the quantities of anti-microbial agents used in food animals, correlations have been demonstrated between the amount of anti-microbial agents used in food animals and anti-microbial resistance in selected bacteria (DANMAP, 2002). The lack of publicly available data on anti-microbial use in food animals in many countries, including the USA, limits such comparisons.

Even in countries without surveillance on anti-microbial use in food animals, temporal associations have been demonstrated between the first approved use of an anti-microbial agent in food animals and an increase in anti-microbial resistance. In the USA, for example, there was a marked increase in the proportion of domestically acquired *Campylobacter* infections that were fluoroquinolone resistant following the first approved use of fluoroquinolones in food animals in 1995 (Smith et al., 1999; Gupta et al., 2003). Similar temporal associations were observed in many European countries, including the Netherlands (Endtz et al., 1990).

Ecological comparisons can also be made between countries that allow use of different anti-microbial agents in food animals. For example, domestically acquired *Campylobacter* infections are commonly fluoroquinolone resistant in European and North American countries that allow use of fluoroquinolones in food animals. However, domestically acquired *Campylobacter* infections are susceptible to fluoroquinolones in Australia, which has not allowed use of fluoroquinolones in food animals (Unicomb et al., 2003).

Molecular subtyping

Molecular subtyping provides important evidence of an association between use of anti-microbial agents in food animals and the anti-microbial-resistant enterococci in humans. Avoparcin, a glycopeptide anti-microbial agent, was approved for use as a growth promoter in Europe in 1974. Use of avoparcin in food animals resulted in emergence and dissemination of vancomycin-resistant enterococci (VRE) in the intestinal tract of the food animals, which was commonly transmitted to humans through the food supply, predominately via contaminated meat and poultry. Before the European ban on avoparcin use as a growth promoter in 1997, Europeans commonly carried VRE in their intestinal tract. Molecular subtyping of VRE isolates isolated from pigs, chickens, healthy humans from the community and from hospitalized patients indicates genetic similarity between the isolates (Bruinsma et al., 2002).

The resistance determinants of VRE are carried on the *Tn*1546 transposon. Importantly, these resistance determinants carry single nucleotide (T or G) variants. Among food animals, the G variants are found only in poultry isolates and the T variants in swine isolates. Among VRE isolates from humans, however, the G and T variants are evenly distributed. Furthermore, human isolates from a Muslim country, where swine are not raised or consumed, carried only the G mutation (Jensen et al., 1998). These data provide compelling evidence of an association between avoparcin use in food animals and carriage of VRE in humans.

Similar molecular evidence is available to suggest an association between use of gentamicin in food animals, particularly chickens and turkeys, in the USA and high-level gentamicin-resistant enterococci in humans. When a gentamicin-resistant gene was present in resistant enterococci from animals, the gene was also present in enterococci isolates from food products of the same animal species. Furthermore, although much diversity was evident among high-level gentamicin-resistant enterococci, indistinguishable strains were found from human and pork isolates, and human and grocery store chicken isolates (Donabedian et al., 2003).

Molecular subtyping is also useful to demonstrate an association between *Salmonella* isolates from animals and humans. In an investigation of an increase of human fluoroquinolone-resistant *Salmonella* Choleraesuis infections in Taiwan, for example, molecular subtyping, including sequencing, allowed investigators to conclude that swine were the source of the human infections; additional investigations suggest that the fluoroquinolone resistance had emerged following fluoroquinolone use in pigs (Chiu et al., 2002).

Review of the Human Health Consequences Resulting from Such Resistance

Evidence is accumulating that anti-microbial resistance among enteric bacteria isolated from humans has human health consequences. This evidence has recently been summarized (Barza, 2002). These human health consequences include: (i) infections that would not otherwise have occurred if the pathogens were not resistant; (ii) increased frequency of treatment failures and (iii) increased severity of infection. Increased severity of infection includes prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization and increased mortality.

Infections that would not have otherwise occurred

The use of anti-microbial agents disturbs the microbiota of the intestinal tract, placing treated individuals at increased risk of clinical salmonellosis, if they are also colonized with a *Salmonella* strain that is resistant to that agent (Barza and Travers, 2002). Individuals taking an anti-microbial agent, for any reason, are therefore at increased risk of developing illness with pathogens resistant to the anti-microbial agent. This effect has been demonstrated in case–control studies of persons infected with anti-microbial-resistant *Salmonella* in which persons exposed to anti-microbial agents for unrelated reasons, such as treatment of an upper respiratory tract infection, are at increased risk of infection with *Salmonella* that is resistant to the anti-microbial agent (Glynn et al., 2004). This effect has also been demonstrated in the laboratory when the use of the antibiotic streptomycin in mice dramatically lowers the dose needed to infect the mouse with a streptomycin-resistant strain (Bohnhoff and Miller, 1962).

This increased risk of *Salmonella* transmission among persons exposed to anti-microbial agents for unrelated reasons can be expressed in the form of an 'attributable fraction', defined as the proportion of *Salmonella* infections that would not have occurred if the *Salmonella* were not resistant (or if the person had not been taking the anti-microbial agent for unrelated reasons). Because of taking anti-microbial agents for a variety of reasons is common in the USA; anti-microbial resistance in *Salmonella* results in infections, hospitalizations and deaths that would not have occurred in the absence of resistance. Barza and Travers (2002) reviewed the literature on 'attributable fraction' and concluded that anti-microbial resistance in *Salmonella* and *Campylobacter* results in 29 379 *Salmonella* infections that would not otherwise have occurred, leading to 342 hospitalizations, 12 deaths and 17 688 *Campylobacter jejuni* infections that would not otherwise have occurred, leading to 95 hospitalizations each year in the USA. A similar effect may occur in food animals, which are also frequently exposed to anti-microbial agents, although the extent that anti-microbial resistance in *Salmonella*, *Campylobacter* and perhaps other bacteria results in increased transmission of these bacteria between food animals that are taking anti-microbial agents has not been described. If such use does promote the spread of resistant strains among food animals, it seems likely that this may result in increased transmission of those strains to humans.

Increased frequency of treatment failures and increased severity of infection

Increased frequency of treatment failures and increased severity of infection may be manifested by prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization or increased mortality. An association between resistance and longer duration of illness has been demonstrated in four recent case–control studies of fluoroquinolone-resistant *Campylobacter* infections (Smith et al., 1999; Neimann et al., 2003; Engberg et al., 2004; Nelson and Angulo, 2004). In these studies, among persons treated with fluoroquinolones, the median duration of diarrhoea in persons infected with fluoroquinolone-resistant *Campylobacter* was several days longer than the median duration of diarrhoea in persons with susceptible infections.

The association between an increased frequency of anti-microbial resistance *Salmonella* and an increased frequency of hospitalization has been demonstrated in several studies. A study of 28 *Salmonella* outbreaks investigated by CDC between 1971 and 1983 found that outbreaks caused by anti-microbial-resistant *Salmonella* resulted in a greater hospitalization rate and greater case-fatality rate than outbreaks caused by susceptible infections (Holmberg et al., 1987).

A study of 758 persons with sporadic *Salmonella* infections in 1989–1990 found that persons infected with anti-microbial-resistant isolates were more likely to be hospitalized longer (Lee et al., 1994). A more comprehensive study of sporadic *Salmonella* infections has recently been completed for the Foodborne Diseases Active Surveillance Network (FoodNet) and National Anti-microbial Resistance Monitoring System (NARMS) in the USA (Varma et al., in press). Unlike the study by Lee et al. (1994), this analysis controlled for the serotype of *Salmonella*. Among *Salmonella* isolates tested in NARMS from 1996 to 2001, *Salmonella* isolates resistant to anti-microbial agents were more frequently isolated from blood than susceptible isolates. A particularly high frequency of isolation from blood was observed among isolates resistant to five or more anti-microbial agents. Among patients interviewed, persons with *Salmonella* isolates resistant to anti-microbial agents were more frequently hospitalized with bloodstream infection than susceptible infections. Again, there was a particularly high frequency of hospitalization with bloodstream infection among persons infected with isolates resistant to five or more anti-microbial agents.

Similarly, a comprehensive study of sporadic *S.* Typhimurium and *Campylobacter* infections has recently been completed in Denmark among patients with culture-confirmed infections from 1995 to 2000 (Helms et al., in press). The Danish Civil Registry System was used to determine patient outcomes. Among patients with *S.* Typhimurium infections, persons with nalidixic acid-resistant infections were more likely to have bloodstream infection or die within 90 days following specimen collection than susceptible infections. Similarly, among persons with *Campylobacter* infections, persons with fluoroquinolone-resistant or erythromycin-resistant infections were more likely to have a bloodstream infection or die within 90 days following specimen collection than susceptible infections.

Treatment failures resulting in death have been rare among *Salmonella* but may be expected to increase as the prevalence of resistance to clinically important anti-microbial agents increases among *Salmonella*. In the best described study of such treatment failures, an outbreak of nalidixic acid-resistant *S.* Typhimurium DT104 in Denmark resulted in the hospitalization of 23 patients and two deaths (Mølbak et al., 1999). Both patients who died had been treated with a fluoroquinolone for their *Salmonella* infections; in both instances, the coroner concluded that the fluoroquinolone resistance contributed to the deaths.

A comprehensive study of mortality associated with anti-microbial resistance among *S.* Typhimurium was recently conducted in Denmark among patients with culture-confirmed infections from 1995 to 1999 (Helms et al., 2002). Again, the Danish Civil Registry System was used to determine patient outcomes and patients were followed for 2 years following culture collection. To determine the increase in mortality compared with the general population, cases were matched to 10 persons from the registry by age, sex, county and co-morbidity. Although persons with susceptible *Salmonella* infections had higher 2-year mortality than the general population, persons with resistant *Salmonella* infections were even more likely to die within 2 years. Furthermore, persons with nalidixic acid-resistant infections and with multidrug-resistant infections had remarkably higher rate of dying in the 2 years following specimen collection than the general population.

Although anti-microbial resistance among *Salmonella* Typhi is not related to use of anti-microbial agents in animals, prolonged duration of illness has also been demonstrated among persons infected with nalidixic acid resistant *S.* Typhi treated with fluoroquinolones. Such apparent treatment failures have been so common among persons infected with strains having borderline MIC to fluoroquinolones that several groups have suggested the breakpoints used to define fluoroquinolone resistance in *Salmonella* and other enteric bacteria should be lowered (Aarestrup et al., 2003; Crump et al., 2003).

Review of Previous WHO/FAO/OIE Consultations and Reports

Many expert panels, including WHO consultations, national committees and independent organizations, have examined the association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans. WHO organized two consultations, in Berlin in 1997 and in Geneva in 1998, to qualitatively assess the risk of human health consequences associated with the use of anti-microbial agents in food-producing animals. The Berlin meeting was entitled 'WHO Consultation on the Medical Impact of Anti-microbial Use in Food Animals'. At this meeting, it was concluded that 'there is direct evidence that anti-microbial use in animals selects for anti-microbial-resistant non-typhoid *Salmonella* serotypes. These bacteria have been transmitted to humans in food or through direct contact with animals (WHO, 1997)'.

The WHO Consultation in Geneva focused on the human health importance of fluoroquinolones and public health concern of increasing resistance to fluoroquinolones, particularly among *Salmonella* and *Campylobacter*, and on the risk of human health consequences associated with the use of fluoroquinolones in food animals. This meeting was entitled 'Use of Quinolones in Food Animals and Potential Impact on Human Health'. It was concluded at this meeting that 'the use of fluoroquinolones in food animals has led to the emergence of fluoroquinolone-resistant *Campylobacter* and of *Salmonella* with reduced susceptibility to fluoroquinolones (WHO, 1998)'.

Similar conclusions have been presented to two committees of the Codex Alimentarius Commission: the Codex Committee on Food Hygiene (CCFH) and Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). A 'Risk profile on anti-microbial-resistant bacteria in food' presented to the 34th session of CCFH in October 2001, stated that: 'Anti-microbials are used in food animals for growth promotion, prophylaxis, metaphylaxis and therapy. This use is the principle contributing factor to the emergence and dissemination of anti-microbial resistance among bacterial pathogens and commensals that have food animal reservoirs (Codex Committee on Food Hygiene, 2001)'. Similarly, a 'Discussion paper on anti-microbial resistance and the use of anti-microbials in animal production' presented to the 13th session of the CCRVDF in July, 2001, stated that: 'Animals serve as reservoirs for food borne pathogens, including *Salmonella* and *Campylobacter*. Antibiotic resistant food borne pathogens may be present in and on animals as a result of drug use in animals. These resistant food borne pathogens may contaminate a carcass at slaughter and can be transmitted to humans through consumption and handling of contaminated food. In industrialized countries, the food borne pathogens, *Salmonella* and *Campylobacter*, are infrequently transferred from person to person. In these countries, epidemiological data have demonstrated that a significant source of antibiotic resistant food borne infections in humans is the acquisition of resistant bacteria originating from animals that is transferred on food (Codex Committee on Residues of Veterinary Drugs in Foods, 2001)'.

Conclusions from these WHO Consultations and presentations to the Codex Alimentarius Commission suggest agreement among scientific experts that use of anti-microbial agents in food animals has resulted in the emergence and dissemination of anti-microbial-resistant bacteria, particularly anti-microbial-resistant *Salmonella* and *Campylobacter* and these bacteria that have been transmitted to humans. This suggests sufficient evidence, particularly among *Salmonella* and *Campylobacter*, to demonstrate an association between use of anti-microbial agents in food animals and anti-microbial resistance among bacteria isolated from humans.

In contrast to the sufficient evidence demonstrating an association between anti-microbial use in food animals and anti-microbial resistance among bacteria isolated from humans, little evidence of human health consequences of such resistance was presented at the WHO consultations or in presentations to the Codex Alimentarius Commission. However, these consultations and presentations focused on treatment failures and did not review the full range of potential adverse human health consequences of such resistance. The consultants at the Berlin meeting in 1997 concluded that 'microbiological and clinical evidence is mounting that resistant bacteria or resistant determinants might be passed from animals to humans resulting in infections that are more difficult to treat', but 'the magnitude of the medical and public health impact of anti-microbial use in food animal production is not known (WHO, 1997)'. The WHO Consultation in Geneva concluded that 'there has been little documented impact of this resistance on human health to date, but there is concern about the potential human health consequences if resistance were to increase and spread. Further research and data gathering are essential to quantify this potential (WHO, 1998)'. More recent evidence, described above, of the human health consequences resulting from anti-microbial-resistant bacteria (that are resistant as a consequence of use of anti-microbial agents in food animals) indicate that the human health impact of such resistance is becoming increasingly more evident.

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